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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,471	08/18/2000	Carol M. Kinoshita	10278-017001	6615

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EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,471	KINOSHITA ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-106 and 109-183* is/are pending in the application.

4a) Of the above claim(s) *81-104 and 172-183* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *105,106,109-171* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed October 22, 2002 inserting the paper copy of the Sequence Listing, amending the specification to insert the reference to the sequence identifiers, canceling claims 107 and 108 and amending claims 105 and 139 has been entered.

"IN RE HAWKINS' Declaration filed October 2, 2002 verifying that the amendatory material consists of the material incorporated by reference has been entered.

Claims 81-106 and 109-183 are pending. Claims 81-104 and 172-183 are withdrawn.

Claims 105, 106 and 109-171 are under consideration.

Drawings

The drawings filed concurrently with the application on August 18, 2000 have been objected by Draftsman, please refer to the attached PTO-948 form for details.

Specification

The use of the trademark has been noted in this application on pages 23; 24; 41-45; page 51, line 16, for example. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Applicant is advised that should claim 129 be found allowable, claim 144 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 165 and 166 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 165 and 166 recite mammalian and human cell, respectively. Claim 139 from which claims 165 and 166 depend is limited to a human cell.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 139-142 and 152-169 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a method of use of "a substance which prevents the removal of at least one mannose residue distal to pentasaccharide core of a precursor oligosaccharide of GCB". Therefore, the claims recite the genus of substances described by function. The specification teaches two inhibitors of human class 1 mannosidase inhibitors: kifunensine and deoxymannojirimycin and four human class 2 mannosidase inhibitors: swainsonine, mannostatin, 6-deoxy-DIM and 6-deoxy-6-fluoro-DIM (page 3, for example). No other substances in addition to human class 1 and 2 mannosidase inhibitors are described in the specification. The specification fails to disclose the correlation between the structure of a substance and the requisite function. Therefore, "a substance which prevents the removal of at least one mannose residue distal to pentasaccharide core of a precursor oligosaccharide of GCB" other than class 1 and 2 mannosidase inhibitors lacks sufficient written description needed to practice the invention of claims 139-142 and 152-169.

Claims 105, 106, 109-132, 137 and 138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human cell comprising a human GCB remodeled to contain terminal mannose residues using mannosidase inhibitors and knockout cells for human mannosidases, does not reasonably provide enablement for a cell that is not capable of expressing a human GCB comprising a precursor oligosaccharide and for a cell that while capable of expressing a human GCB comprising a precursor oligosaccharide is not affected by kifunensine or a knockout non-human cell for mannosidase of unknown structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is drawn to remodeling of oligosaccharide chains of human GCB. Claims are drawn to using an inhibitors of human mannosidase in a cell expressing human GCB. The specification provides no guidance as to which cells would express

human GCB with the correct oligosaccharide precursor and which cells other than human are responsive to inhibitors of human mannosidases. There is no teaching as to how to make a knockout cell for mannosidase of an unknown structure.

With regard to claims 125-126, the specification is enabled only for cells which comprise a class 2 processing mannosidase of a known structure such as human cells. Without knowing the structure of a mannosidase, it is impossible to make a knockout gene or an antisense molecule.

The specification teaches the preparation of human GCB comprising high mannose glycans such as $Man_9GlcNAc_2$ (31.2%), $Man_8GlcNAc_2$ (32%) and $Man_7GlcNAc_2$ (23.3%) using human fibroblast HT-1080 cells treated with kifunensine (page 55, Table 3). In this cells the GCB is endogenous to the cells and the regulatory sequence is exogenous.

This result is specific for the specific reaction occurring in these cells under the specific experimental conditions. It is unpredictable as to how many mannose residues will retain on a GCB present in a different type of cell under the same conditions.

In fact, the art teaches that GCB expressed in insect SF9 cells contains a single species of the oligosaccharides $Man_3GlcNAc(Fuc)GlcNAc$ (US Patent 5,236,838, column 13, lines 18-50, form PTO-1449 filed November 30, 2000, reference AC). Thus, searching for conditions that would lead to obtaining a hmGCB specifically quantitatively remodeled using any cell comprising any GCB is well outside the realm of

routine experimentation and predictability in the art of success is extremely low. One skilled in the art would require additional guidance, such as information regarding the type of cell capable of expressing a human GCB comprising a precursor oligosaccharide that is affected by kifunensine. Without such a guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 105, 106 and 109-171 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite "hmGCB'. The specification defines the term "hmGCB" by non-limiting examples (page 15, line 25 through page 16, line 22) rendering the metes and bounds of the term unascertainable.

Claims 125 and 151 are confusing as reciting "at least one class 2 processing mannosidase" (emphasis added).

Claim 139 reads on any regulatory sequence that can be incorporated into any gene not necessarily the GCB gene, that for any reason, directly or indirectly can affect the expression of an endogenous GCB.

Claims not specifically rejected are rejected as dependent from the rejected base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 105, 106 and 109-171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedman et al. in view of Smith et al.

Claims 105, 106, 109-132, 137 and 138 are included in this rejection as encompassing the embodiment of human cells expressing human GCB.

Friedman et al. (US Patent 5,549,892, form PTO-1449 filed November 30, 2000, reference AD) teach the importance of a glycoprotein, human GCB, needed for treatment of Gaucher's disease. They teach the importance of GCB remodeling for the production of a pharmaceutically effective preparation and the production of a remodeled recombinant human GCB in CHO cells. The sequence encoding human GCB comprises exogenous regulatory and coding sequences (columns 3-4). Friedman et al. teach that the remodeling of the carbohydrate chains may be accomplished by

several different alternative ways such as utilizing mutant cell lines deficient in certain carbohydrate synthetic pathways (column 6, lines 1-15).

Smith et al. (US Patent 5,939,279) teach the method of preparing high mannose $Man_9(GlcAc)_2$ glycoproteins by treating human HT-29 cells with mannosidase I inhibitors, deoxymannojirimycin or kifunensine (columns 7-8, column 9, claim 8). With regard to claims 109 and 110, Smith et al. teach the required range of the kifunensine concentration (column 8, lines 24 and 25). With regard to claims 111-114, Smith et al. teach the required range of the swainsonine concentration (column 8, line 26). One of the glycoproteins present in HT-29 cells is GCB.

Therefore, at the time the invention was made, the importance of remodeling GCB to produce hmGCB has been known. The mannosidase inhibitors as tools to prepare human hmGCB have been known. The genetic manipulation of protein expression and techniques to make a knockout gene of a known structure and antisense molecule therefor were known.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare hmGCB obtained from HT-29 or other human cells using method of Smith et al. One of ordinary skill in the art at the time the invention was made would have been motivated to specifically purify GCB in view of its importance taught by Friedman et al. The high expectation of success is provided by Smith et al. who teach the requisite step for preparing remodeled glycoproteins while

the purification of proteins from the cells is standard in the art and is taught by Friedman et al., for example.

With regard to claims 127, 128 and 139-171 it would have been obvious to increase the production of GCB in the cells by the introduction of additional copies of a GCB gene and/or by introducing the exogenous regulatory sequence that would increase the expression of GCB. Such techniques are standard in the art and are widely used for the increased production of the proteins of interest.

Response to Arguments

Applicant's arguments filed October 22, 2002 have been fully considered but they are not persuasive.

With regard to the enablement Applicants argue that they enabled the production of human hmGCB in view of the data obtained with HT-1080 cells. As discussed above, the production of human hmGCB in human cells is enabled but is not enabled in other types of cells. With regard to knockout cells, Applicants argue that the structures for human mannosidases are known ans therefore such cells are enabled (pages 9-11). The examiner agrees that human knockout cells are enabled but other cells for which the structure is unknown are not. Further, it is unknown whether kifunensine and other inhibitors of human mannosidases inhibit mannosidases of other origins.

With regard to the 103(a) rejection Applicants argue that Smith does not mention glucocerebrosidase at all and that Friedman does not disclose or suggest using kifunensine (page 16). This is not persuasive because the rejection is 103 not 102 and therefore does not need to contain all elements of the invention but has to make it obvious. As discussed above, Smith et al.teach the requisite remodeling of human glycoproteins without specifically mentioning GCB. The motivation to use the teachings of Smith et al. to prepare hmGCB steams for the importance of such preparation obtained by any available method as taught by Friedman et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

January 10, 2003